FACT SHEET

Pembrolizumab

Key words

- Drug class: antibody targeting cellular programmed cell death protein-1 (PD-1)
- Molecule: humanised monoclonal IgG4 antibody
- Binding/inhibiting/MoA: binds PD-1 to block it from its ligands so that T-cell can attack tumor cells
- Originator brand name: Keytruda®

Molecule

Pembrolizumab (Keytruda®) is a humanized monoclonal IgG4 antibody that contains an engineered hinge region mutation (S228P). It has a moolecular weight of 146.3 kDa and is targeted to the cellular programmed cell deth protein-1 (PD-1).

Mode of Action

Programmed cell death ligand 1 or ligand 2 (PD-L1 or PD-L2) is upregulated on 40-50 % of melanomas and has limited expression otherwise. Both ligands bind to PD-1, a protein on the surface of activated T-cells. If PD-L1 binds to PD-1, a T-cell becomes inactive and inhibited from attacking a tumor. The inhibitory effect results from the promotion of apoptosis in antigen-specific T-cells while simultaneously blocking apoptosis in suppressor T-cells. Pembrolizumab binds to PD-1, thus blocking PD-L1 or PD-L2 from binding to PD-1, and T-cells can again attack tumor cells.

Indication

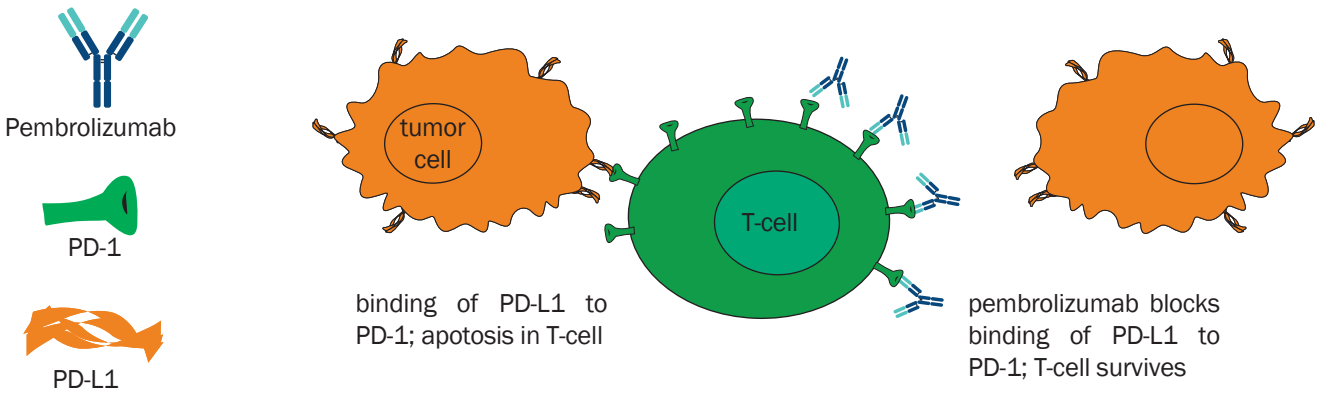
Keytruda® is indicated for more than 30 cancer types, such as melanoma, non-small cell lung cancer, head and neck squamous cell cancer, classical Hodgkin lymphoma, gastric cancer, cervical cancer, hepatocellular carcinoma, and primary mediastinal large B-cell lymphoma.

Patent Situation

Patents for Keytruda® have expiry dates of up to 2036 in the US and 2028 in the EU. Bristol Myers Squibb (BMS) owns patents directed to the inhibition of PD-1 and is filing lawsuits against competitors marketing antibodies with this target. This also included Keytruda®, resulting in royalty payments of Merck Sharp & Dohme (MSD).

Market and Competitive Field

Keytruda® from MSD was approved for its first indication by FDA in 2014 and by EMA in 2015. In 2023, MSD had sales for Keytruda® of 23.5 billion €, up from 19 billion € in 2022. Due to late patent expiry dates and the development of novel antibodies also targeting PD-1, there are currently no biosimilars in late stage of clinical development.



binding of PD-L1 to PD-1; apotosis in T-cell

pembrolizumab blocks binding of PD-L1 to PD-1; T-cell survives

vela LABORATORIES
A Tentamus Company

v Installed at VelaLabs under GxP ○ Analytical concept exists/installed under R&D

Pembrolizumab: selected GMP, GLP, GCLP methods

Characterisation of the molecule & GxP techniques

CBA - CELL BASED ASSAYS

- v PD-L1 blockade reporter gene assay
- v PD-L2 blockade reporter gene assay
- v ADCC (negative assay)
- v ADCP (negative assay)
- v CDC (negative assay)

PCM - PHYSICOCHEMICAL ASSAYS

- ○ Size exclusion HPLC
- ○ Ion exchange HPLC
- ○ Reversed phase HPLC
- ○ SDS-PAGE
- ○ Western blot
- ○ PCR (Polymerase Chain Reaction)
- ○ Capillary electrophoresis
- ○ cIEF (capillary isoelectric focusing)

LBA - LIGAND BINDING ASSAYS

- v Binding ELISA
- v Competition ELISA
- ○ Host Cell Protein (HCP) ELISA
- v Affinity to PD-1 (SPR)
- v Fc Receptor affinity (SPR)
- ○ Lectin Array Glycoprofiling

COMPENDIAL PCM METHODS (EP & USP)

- ○ pH measurement (EP 2.2.3)
- ○ Appearance (EP 2.2.1)
- ○ Turbidity (EP 2.2.1)
- ○ Colour of solution (EP 2.2.2)
- ○ Osmolality (EP 2.2.35)
- ○ Visible particles (2.9.20)
- ○ Subvisible particles (2.9.19)
- ○ Extractable volume (EP 2.9.17)
- ○ Protein concentration by OD280 (EP 2.5.33)

(PRE-) CLINICAL ANALYTICS under G(C)LP

- ○ PD - Pharmacodynamics
- ○ PK - Pharmacokinetics
- ○ ADA - Anti-Drug Antibody testing
- ○ Biomarker studies

MICROBIOLOGY / SAFETY

- v Sterility (EP 2.6.1)
- v Endotoxin, gel-clot limit test (EP 2.6.14)
- v Endotoxin, chromogenic LAL test (EP 2.6.14)
- v Endotoxin, recombinant Factor C (EP 2.6.32)